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Letter to the Editor

In-Depth Genetic and Functional Studies are Required to Establish a Causal Link between Copy Number Variants and Mental Health Disorders

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Letter to the Editor

We read with interest the article by Arendt *et al*. on the frequency, type and inheritance of copy number variants (CNVs) associated with mental disorders (MHDs) such as schizophrenia (SCZ), bipolar disorder (BD), major depressive disorder (MDD), anxiety disorder (AXD) and attention deficit hyperactivity disorder (ADHD) in 2152 patients and 866 parents from the Brazilian High Risk Mental Health Cohort Study (BHRCS) [1]. Most of the CNVs detected were rare and 56% were inherited [1]. Of 40 CNVs already known to be associated with MHD, 18 were identified in the index sample [1]. Duplications in 2q13 and 15q13.3 showed a lower frequency, while duplications in 2q11.2 and 16p11.2 showed a higher frequency compared to previous results [1]. The 7q11.2 deletion was found to be protective for MHD [1]. The study is noteworthy, but some points should be discussed.

The first point is that the causal relationship between CNVs and MHD has not been proven. Since the significance of CNVs may be unknown or they may be expressed with incomplete penetration [2], appropriate studies must be conducted to determine whether a specific CNV has an impact on protein structure, enzyme activity, transport function, signalling, pore function, cell morphology, vesicle transport, or reproduction [3].

The second point is that CNVs can lead not only to MHD but also to numerous other phenotypic manifestations. These include epilepsy, spasticity, ataxia, dementia, muscle hypotonia, but also heart disease, gastrointestinal disorders, endocrine disorders and renal dysfunction [4, 5]. Therefore, we should know what abnormalities other than SCZ, BD, AXD or ADHD have been detected in the included patients. Knowledge of comorbidities is important as they can strongly influence the severity and course of MHD. In particular, structural and functional cerebral diseases can strongly influence the course and outcome of MHDs [6, 7]. According to Table 1, 9 CNVs were accompanied by developmental disorders that should be specified to establish a genotype-phenotype correlation [1].

The third point is that cerebral imaging, electroencephalography (EEG) or CSF studies were not performed in the included patients to assess whether CNVs also led to structural and functional cerebral lesions or whether causes other than CNVs were responsible for the analyzed MHDs. Knowing whether structural or functional lesions are present in patients with MHD is of crucial importance as it can strongly influence therapy and outcome in these patients. Phenotypic expression in organs other than the brain would support a causal relationship between CNVs and MHD.

The fourth point relates to the frequency of inherited CNVs [1]. Since in more than half of the patients the CNVs were inherited from one parent, we should know whether the affected parents also manifested phenotypically with the same clinical appearance as their offspring. How many of the MHD patients had parents who also suffered from MHD and carried the same CNV as their children?

The fifth point is that it was not explained why CNVs, which are known to be associated with MHD, were only looked for in the mothers of the probands and not in their fathers. We should know how many of the fathers carrying CNVs or not had MHD. The reasoning that in 91% of the patients the mothers were the caregivers and therefore only the maternal phenotype was associated with the CNVs is not valid, as the children may have inherited the CNVs from their father as often as from their mother.

The sixth point is that it is not understandable why subjects with and without MHD (n=958) and subjects without psychiatric symptoms but with high familial clustering of psychiatric symptoms (n=1553) were included. As the study aimed to investigate the frequency of CNVs in subjects with MHD, those without MHD should be excluded from the study.

Finally, the implications of the results for genetic counseling and family planning were not discussed in great detail. As 56% of

CNVs were inherited, it is crucial to inform and guide parents with regard to future pregnancies.

In conclusion, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. Cerebral examinations are needed in patients with MHD due to CNVs to determine whether CNVs also cause structural cerebral lesions (e.g. diffuse, or cortical cerebral atrophy, cortical, subcortical or white matter alterations, microcephaly, microcephalus) and to rule out alternative causes of MHD.

Declarations

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